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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/540,228 | 06/21/2005 | Ernest Loumaye | KZI-001US | 1620 |

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| EXAMINER | |
|---|---|
| MOHAMED, ABDEL A | |

| ART UNIT | PAPER NUMBER |
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| 1654 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/540,228 | LOUMAYE, ERNEST | |
| | Examiner | Art Unit | |
| | Abdel A. Mohamed | 1654 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *73 and 75-103* is/are pending in the application.

4a) Of the above claim(s) *102 and 103* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *73 and 75-101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/22/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

## ACKNOWLEDGEMENT TO PRIORITY, AMENDMENT, REMARKS, RESPONSE TO RESTRICTION REQUIREMENT, IDS, STATUSOF THE APPLICATION AND CLAIMS

1. This application is filed under 35 U.S.C. 371 on 06/21/05 having a filing date of 12/29/03 of PCT/IB03/06205. Acknowledgement is made of Applicant's claim for priority based on French Application No. 0216810 having a filing date of 12/27/02. Receipt is acknowledged of papers submitted under 35 U.S.C. § 119, which papers have been placed of record in the file. The amendment, remarks, response to restriction requirements filed 10/15/08 and the information disclosure statement (IDS) and Form PTO-1449 filed 08/22/05, respectively are acknowledged, entered and considered. In view of Applicant's request claims 73, 75, 85, 88, 90, 93 and 102 have been amended and claim 74 has been canceled. Claims 73 and 75-103 are now pending in the application.

## OBJECTION TO THE SPECIFICATION

2. The specification is objected because there are no Headings disclosed in the disclosure and the following guidelines illustrate the preferred layout and content for patent application. These guidelines are suggested for the Applicant's use.

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.

(b) CROSS-REFERENCE TO RELATED APPLICATIONS.

(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.

(d) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) Or

REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)

(e) BACKGROUND OF THE INVENTION.

(1) Field of the Invention.

(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.

(f) BRIEF SUMMARY OF THE INVENTION.

(g) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).

(h) DETAILED DESCRIPTION OF THE INVENTION.

(i) CLAIM OR CLAIMS (commencing on a separate sheet).

(j) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).

(k) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

The specification is also objected on page 1, line 15 in the recitation "a hormone call FSH" and on page 2, lines 19 and 20 and page 5, line 28 in the recitation "Assisted Reproductive Technics". It is believed to be typographical errors. Appropriate correction is required.

**ELECTION WITH TRAVERSE**

3. Applicant's election with traverse of Group I (claims 73-101) based on the original restriction described in the Office action of 08/29/07 in the reply filed 10/15/08 is acknowledged and is found to be persuasive, and as *per* Applicant's request, the election requirements for claims 73 and 75-101 including the election of species requirements thereof are withdrawn in view of Applicant's traverse. Therefore, claims 102 and 103 are withdrawn as non-elected invention since they are drawn to a kit claims and the Office action is directed to the merits of claims 73 and 75-101 as *per*-elected invention.

## CLAIMS REJECTION-35 U.S.C. 112, 1st PARAGRAPH

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 83, 84 and 90-94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. There is no description in the instant specification for the claimed method for **treating infertility** in a female mammal comprising administering a pharmaceutical agent comprising GnRH agonist, wherein the pharmaceutical agent which supports the luteal phase is administered in combination with a **cytokine** involved in embryo implantation mechanisms, wherein the cytokine is selected from the group consisting of native Leukemia Inhibitor Factor (LIF), recombinant LIF, a peptidic or a non-peptidic agonist analog of LIF, and a combination thereof (claims 83 and 84). Similarly, there is no description for the claimed method for **treating infertility** in a female mammal comprising administering a pharmaceutical agent comprising GnRH agonist, wherein the pharmaceutical agent which supports the luteal phase is administered in combination with a **selective estrogen receptor**

**modulators (SERM)**, **aromatases inhibitors**, **phosphodiesterase inhibitors**, and a combination of two or more of these agents (claim 90), wherein the SERM is selected from the group consisting of tamoxifen(e), ralooxifen(e), and a combination of two or more of these agents (claim 91), wherein the aromatase inhibitor is selected from the group consisting of anastrozole, letrozole, exemestane, and a combination of two or more of these agents (claim 92), and wherein the phosphodiesterase inhibitor is theophyline (claim 94).

Examples 1 and 2 in the instant specification demonstrate the effect of the method of treating infertility by administering GnRH agonist in combination with hCG, or busereline, or FSH, or clomiphene citrate for maintaining the luteal phase after inducing follicular development and ovulation in patients suffering from unexplained infertility, or from infertility resulting from mild to moderate endometriosis, or an infertility resulting from a mild or moderate alteration of their partner sperm, and whom have not conceived despite regular sexual intercourses during a period of one or two years, usually undergo medical assistance. Also, patients who were pregnant after 3 to 6 cycles of IUI, were proposed a treatment with IVF or ICSI.

However, there is no infertility treatment by administering the claimed pharmaceutical agents of claims 83, 84 and 90-94. to support the luteal phase. Although, numerous protocols have been intended to be utilized with these agents of which only the definition are disclosed or described on pages 7 and 12 in the instant specification. Nevertheless, there is no *in vivo* or *in vitro* showing or data or a single example to demonstrate for the effectiveness of the method for using the claimed

pharmaceutical agents to support the luteal phase during infertility treatment. Thus, the instant specification provide very little guidance in regard to making/using the claimed pharmaceutical agents for treating infertility in the manner claimed in claims 83, 84 and 90-94. Therefore, in the express absence of one or more examples, evidence and sufficient guidance, the skilled artisan would be faced with undue experimentation for practicing the invention as claimed in claims 83, 84 and 90-94.

## CLAIM REJECTIONS-35 U.S.C. § 102(b)

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) The invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 73, 75-82, 85-90, 95, 99 and 101are rejected under 35 U.S.C. 102(b) as being anticipated by Jacobs (US Patent No. 5,538,948).

The Jacobs reference ('948 patent) discloses a method for treating infertility such as polycystic ovaries (PCO) generally in female mammal and particularly in women by administering an effective amount of GnRH agonist in combination with gonadotrophins or growth hormones or follicular stimulating hormones or lutenizing hormones (See e.g., abstract and col. 1). The '948 patent on col. 2 states that the cause of infertility in women include: 1) Abnormal ovarian function (primary ovarian failure). 2) Reduced hypothalamic-pituitary function, i.e., pituitary insufficiency, causing ovulatory failure

(Secondary ovarian failure). 3) Tubal damage (adhesions, obstructions, etc.). 4) Endometriosis (the presence of membranous material of the kind lining the uterus at other sites within the cavity of the pelvis). 5) Unexplained infertility.

Further, the '948 patent is based on the surprising discovery that in a treatment for *in vitro* fertilization (IVF) or *in vivo* fertilization with gonadotrophins the ovarian response is highly augmented when the gonadotrophins are combined with as well a GnRH analogue as growth hormone. In this way, a dramatic increase of the probability for obtaining fertilized eggs in IVF is achieved in comparison with a treatment with either a combination of GnRH analogues and gonadotrophins or a combination of gonadotrophins and growth hormone. Examples of useful GNRH analogues which may be either a GnRH analogue antagonist or a GnRH analogue agonist are buserelin, triptorelin and leuprolide acetate. The administration of the components may be by intravenous, intramuscular or subcutaneous route. Other routes of administration which may establish the desired blood levels of the respective components are comprised by the present invention. In order to obtain mutifollicular development in human individuals, the individual is preferably treated with 2-40 mg buserelin, 500-20000 IU gonadotrophins and 2-160 IU hGH, administered in a number of daily doses and the optimal amount being 3-20 mg buserelin, 1000-12000 IU gonadotrophins and 12-144 IU hGH (See e.g., col. 3 and claims 3-9).

In Example 1, the '948 patent discloses the protocol of combined treatment of GH and buserelin/hMG in which the GnRH analogue buserelin was injected daily for downregulation of the ovaries from mid luteal phase of the previous cycles. When the

ovaries were downgraded i.e., low estrogen level and no follicles, treatment with gonadotrophins (i.e., hMG) was initiated. The dose of hMG was individually adjusted according to ovarian response and hCG was administered. 35 hours later oocytes were recovered for fertilization, and embryos (or oocytes) were transferred back 2-3 days later (or sooner if oocytes were transferred). Thus, meeting the limitations of claim 73 as well as claims dependent thereof (i.e., claims 75-82, 85-90, 95, 99 and 101) by clearly showing the administration of GnRH agonist to female mammal within the first three days either after a spontaneous ovulation or after stimulation of follicular growth and triggering of final follicular maturation and ovulation in the female mammal with at least one additional agent to treat infertility in female mammal.

Therefore, the prior art discloses a method of treating infertility in a female mammal by administering GnRH agonist such as buserelin in combination with gonadotrophins to support luteal phase during *in vitro* fertilization or *in vivo* fertilization treatment in the manner claimed in claims 73, 75-82, 85-90, 95, 99 and 101 and as such the prior art anticipates the claims as drafted.

## CLAIMS REJECTION-35 U.S.C. § 103(a)

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 73, 75-82, 85-90 and 95-101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobs (U.S. Patent No. 5,538,948) taken with Schmidt-Sarosi et al (J. Assisted Repro. Gen., Vol. 12, No. 3, pages 167-174, 1985) cited by Applicant on IDS filed 08/22/05.

The reference of Jacobs ('948 patent) as discussed above under the rejection 102(b) discloses a method for treating infertility such as polycystic ovaries (PCO) generally in female mammal and particularly in women by administering an effective amount of GnRH agonist in combination with gonadotrophins or growth hormones or follicular stimulating hormones or lutenizing hormones (See e.g., abstract and col. 1). The '948 patent on col. 2 states that the cause of infertility in women include: 1) Abnormal ovarian function (primary ovarian failure). 2) Reduced hypothalamic-pituitary function, i.e., pituitary insufficiency, causing ovulatory failure (Secondary ovarian failure). 3) Tubal damage (adhesions, obstructions, etc.). 4) Endometriosis (the presence of membranous material of the kind lining the uterus at other sites within the cavity of the pelvis). 5) Unexplained infertility.

Further, the '948 patent is based on the surprising discovery that in a treatment for *in vitro* fertilization (IVF) or *in vivo* fertilization with gonadotrophins the ovarian response is highly augmented when the gonadotrophins are combined with as well a GnRH analogue as growth hormone. In this way, a dramatic increase of the probability for obtaining fertilized eggs in IVF is achieved in comparison with a treatment with either a combination of GnRH analogues and gonadotrophins or a combination of

gonadotrophins and growth hormone. Examples of useful GNRH analogues which may be either a GnRH analogue antagonist or a GnRH analogue agonist are buserelin, triptorelin and leuprolide acetate. The administration of the components may be by intravenous, intramuscular or subcutaneous route. Other routes of administration which may establish the desired blood levels of the respective components are comprised by the present invention. In order to obtain mutifollicular development in human individuals, the individual is preferably treated with 2-40 mg buserelin, 500-20000 IU gonadotrophins and 2-160 IU hGH, administered in a number of daily doses and the optimal amount being 3-20 mg buserelin, 1000-12000 IU gonadotrophins and 12-144 IU hGH (See e.g., col. 3 and claims 3-9).

In Example 1, the '948 patent discloses the protocol of combined treatment of GH and buserelin/hMG in which the GnRH analogue buserelin was injected daily for downregulation of the ovaries from mid luteal phase of the previous cycles. When the ovaries were downgraded i.e., low estrogen level and no follicles, treatment with gonadotrophins (i.e., hMG) was initiated. The dose of hMG was individually adjusted according to ovarian response and hCG was administered. 35 hours later oocytes were recovered for fertilization, and embryos (or oocytes) were transferred back 2-3 days later (or sooner if oocytes were transferred). Thus, meeting the limitations of claim 73 as well as claims dependent thereof (i.e., claims 75-82, 85-90, 95, 99 and 101) by clearly showing the administration of GnRH agonist to female mammal within the first three days either after a spontaneous ovulation or after stimulation of follicular growth

and triggering of final follicular maturation and ovulation in the female mammal with at least one additional agent to treat infertility in female mammal.

The primary reference of Jacobs ('948 patent) differs from claims 96-98 and 100 in not teaching the administration of buserelin intra-nasally at a dose between 50 and 600 µg (claim 96) or at a dose of 200 µg (claim 97) or at a dose between 50 and 400 µg (claim 98) or at a dose of 100 µg (claim 100). Although, the primary reference teaches the administration of buserelin between 2-40 mg for treatment of infertility, however, the secondary reference of Schmidt-Sarosi et al discloses the administration of GnRH agonist such as nafarelin which is equivalent to buserelin at a dose of 400 µg intra-nasally for the treatment of infertility (See e.g., abstract; page 168, second col., paragraph 3; and page 173, first col., paragraph 3).

Therefore, in view of the above, it would have been obvious to one of ordinary skill in the art to which this invention pertains to combine the secondary reference's teachings (i.e., intra-nasal administration of nafarelin/buserelin at a dose of at least 400 µg) for the same purposes into the primary reference's teachings because such features are known and suggested in the art as seen in the secondary reference, and including such features of intra-nasal administration of 400 µg of nafarelin/buserelin as taught by the secondary reference of Schmidt-Sarosi et al into the primary reference of Jacobs would have been obvious to one of ordinary skill in the art to obtain the known and recognized functions and advantages thereof. Further, it is conventional and within the skill of the art to which this invention pertains to employ any additional adjustment that may be needed with respect to dosages (i.e. such as adjusting the buserelin formulation

at lower doses). It would simply be to optimize the dosage for the intended recipient since the prior art teaches making and using the formulation for therapeutic use to treat infertility. Thus, such optimization clearly would be routine to persons of ordinary skill in the art to which this invention pertains. Therefore, in view of the above and the combined teachings of the prior art, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, absent of sufficient objective factual evidence or unexpected results to the contrary.

## CITATION OF RELEVANT PRIOR ART

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Lunenfeld (U.S. Patent No. 6,489,288 B1) teaches the administration of GnRH analogues and estrogen in the treatment of polycystic ovarian disease (PCOD) and associated infertility.

## CONCLUSION AND FUTURE CORRESPONDANCE

9. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272-0955. The examiner can normally be reached on First Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mohamed/A. A. M./
Examiner, Art Unit 1654

/JON P WEBER/
Supervisory Patent Examiner, Art Unit 1657